

As set forth above, the DE '287 and US '685 references, alone and in combination, fail to teach or suggest all the claim limitations. Further, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references as required by Applicants' claims

Accordingly, claims 1 and 11 are patentable over the DE '287 and US '685 references. Claims 2-7, 9, 12-14, 21-24, 35, 39-41 and 44-46 depend from claims 1 and 11 and, likewise, are patentable over the DE '287 and US '685 references.

CONCLUSION

Reconsideration and allowance of claims 1-7, 9, 11-14, 21-24, 35, 39-41 and 51-82 is respectfully requested in view of the foregoing discussion. This case is believed to be in condition for immediate allowance. Applicant respectfully requests early consideration and allowance of the subject application.

Applicants conditionally petition for an extension of time to provide for the possibility that such a petition has been inadvertently overlooked and is required. As provided below charge Deposit Account No. **04-1105** for any required fee.

Should the Examiner wish to discuss any of the amendments and/or remarks made herein, the undersigned attorney would appreciate the opportunity to do so.

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Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE IN CLAIMS

Please note that additions to the claims are shown underlined and deletions are shown in brackets.

1. A formulation comprising penetrants being capable of penetrating the pores of a barrier, even when the average diameter of said pores is smaller than the average diameter of said penetrants, wherein said penetrants can transport agents or enable agent penetration through said pores after said penetrants have entered said pores, wherein the formulation further comprises

at least one consistency builder in an amount that increases the formulation viscosity above that of the non-thickened corresponding formulation to maximally 5 Ns/m² so that spreading over, and retention at, the application area is enabled, or

at least one antioxidant in an amount that reduces the increase of oxidation index to less than 100% per 6 months, or

at least one microbiocide in an amount that reduces the bacterial count of 1 million germs added per gram of total mass of the formulation to less than 100 in the case of aerobic bacteria, to less than 10 in the case of entero-bacteria, and to less than 1 in the case of Pseudomonas aeruginosa or Staphilococcus aureus, after a period of 4 days

wherein the relative content of agents is above 0.1 weight-%, relative to total dry mass of the formulation.

5. The formulation according to claim 1, wherein the consistency builder is selected from the group consisting of:

pharmaceutically acceptable hydrophilic polymers[, including partially etherified cellulose derivatives, comprising carboxymethyl-, hydroxyethyl-, hydroxypropyl-, hydroxypropylmethyl-, or methyl-cellulose];

completely synthetic hydrophilic polymers [including polyacrylates, polymethacrylates, poly(hydroxyethyl)-, poly(hydroxypropyl)-, poly(hydroxypropylmethyl)methacrylate,

polyacrylonitrile, methallyl-sulphonate, polyethylenes, polyoxiethylenes, polyethylene glycols, polyethylene glycol-lactide, polyethylene glycol-diacrylate, polyvinylpyrrolidone, polyvinyl alcohols, poly(propylmethacrylamide), poly(propylene fumarate-co-ethylene glycol), poloxamers, polyaspartamide, (hydrazine cross-linked) hyaluronic acid, silicone];

natural gums [including alginates, carrageenan, guar-gum, gelatine, tragacanth, (amidated) pectin, xanthan, chitosan collagen, agarose]; and

mixtures and further derivatives or co-polymers thereof.

7. The formulation according to claim 1, wherein the anti-oxidant is selected from the group consisting of:

synthetic phenolic antioxidants[, including butylated hydroxyanisol (BHA), butylated hydroxytoluene (BHT) and di-tert-butylphenol (LY178002, LY256548, HWA-131, BF-389, CI-986, PD-127443, E-5119, BI-L-239XX), tertiary butylhydroquinone (TBHQ), propyl gallate (PG), 1-O-hexyl-2,3,5-trimethylhydroquinone (HTHQ)];

aromatic amines[, including diphenylamine, p-alkylthio-o-anisidine, ethylenediamine derivatives, carbazol and tetrahydroindenoindol];

phenols and phenolic acids[, including guaiacol, hydroquinone, vanillin, gallic acids and their esters, photocatchuic acid, quinic acid, syringic acid, ellagic acid, salicylic acid, nordihydroguaiaretic acid (NDGA), eugenol];

tocopherols and their derivatives [including tocopheryl-acrylate, -laurate, myristate, -palmitate, -oleate, -linoleate, or any other suitable tolopheryl-lipoate, tocopheryl-POE-succinate];

trolox and corresponding amide and thiocarboxamide analogues;

ascorbic acid and its salts, isoascorbate, (2 or 3 or 6)-o-alkylascorbic acids, ascorbyl esters[, including 6-o-lauroyl, myristoyl, palmitoyl-, oleoyl, or linoleoyl-L-ascorbic acid];

non-steroidal anti-inflammatory agents (NSAIDs)[, such as indomethacine, diclofenac, mefenamic acid, flufenamic acid, phenylbutazone, oxyphenbutazone acetylsalicylic acid, naproxen, diflunisal, ibuprofene, ketoprofene, piroxicam, penicillamine, penicillamine disulphide, primaquine, quinacrine, chloroquine, hydroxychloroquine, azathioprine, phenobarbital, acetaminephen];

aminosalicylic acids and derivatives;

methotrexate, probucol, antiarrhythmics[, including amiodarone, aprindine, asocainol];
ambroxol, tamoxifene, b-hydroxytamoxifene;
calcium antagonists[, including nifedipine, nisoldipine, nimodipine, nicardipine,
nilvadipine], beta-receptor blockers [including atenolol, propranolol and nebivolol];
sodium bisulphite, sodium metabisulphite, thiourea;
chellating agents[, including EDTA, GDTA, desferral];
miscellaneous endogenous [defence] defense systems[, including transferrin, lactoferrin,
ferritin, cearylplasmin, haptoglobin, haemopexin, albumin, glucose, ubiquinol-10];
enzymatic antioxidants[, including superoxide dismutase] and metal complexes with a
similar activity[, including catalase, glutathione peroxidase], and less complex molecules[,
including beta-carotene, bilirubin, uric acid];
flavonoids [including flavones, flavonols, flavonones, flavanones and chalcones,
anthocyanins];
N-acetylcystein, mesna, glutathione, thiohistidine derivatives, triazoles;
tannins, cinnamic acid, hydroxycinnamic acids and their esters[, including coumaric
acid and esters, caffeic acid and their esters, ferulic acid, (iso-)chlorogenic acid, sinapic acid];
spice extracts[, including spice extracts from clove, cinnamon, sage, rosemary, mace,
oregano, allspice and nutmeg];
carnosic acid, carnosol, carsolic acid; rosmarinic acid, rosmaridiphenol, gentisic acid,
ferulic acid;
oat flour extracts[, including avenanthramide 1 and 2]; thioesters, dithioesters,
sulphoxides, tetralkylthiuram disulphides;
phytic acid, steroid derivatives[, including U74006F]; and
tryptophan metabolites[, including 3-hydroxykynurenine and 3-hydroxyanthranilic acid]
and organochalcogenides.

9. The formulation according to claim 1, wherein the microbiocide is selected from the
group consisting of:

short chain alcohols[, including ethyl and isopropyl alcohol, chlorobutanol, benzyl
alcohol, chlorobenzyl alcohol, dichlorobenzylalcohol, hexachlorophene];

phenolic compounds[, including cresol, 4-chloro-m-cresol, p-chloro-m-xlenol, dichlorophene, hexachlorophene, povidon-iodine];

parabenes[, including alkyl-parabenes, including methyl-, ethyl-, propyl-, or butyl-paraben, benzyl paraben];

acids[, including sorbic acid, benzoic acid] and their salts;

quaternary ammonium compounds[, including alkonium salts, benzalkonium salts, including a chloride or a bromide, cetrimonium salts, phenoalkecinium salts, including phenododecinium bromide, cetylpyridinium chloride] and other salts;

mercurial compounds[, including phenylmercuric acetate, borate, or nitrate, thiomersal, chlorhexidine or its gluconate, and mixtures thereof].

11. [The] A formulation comprising penetrants being capable of penetrating the pores of a barrier, even when the average diameter of said pores is smaller than the average diameter of said penetrants, wherein said penetrants can transport agents or enable agent penetration through said pores after said penetrants have entered said pores, the agents associated with said penetrants being corticosteroids, [especially glucocorticoids or mineralocorticosteroids,] wherein the relative content of corticosteroids is above 0.1 weight-%, relative to total dry mass of the formulation.

39. The formulation according to claim 35, wherein the relative content of corticosteroids is the case of clobetasol or one of its derivatives, [such as propionate,] is below 15 w-%, relative to total dry mass of the drug-loaded carriers.

Please add the following new claims:

51. The formulation according to claim 5, wherein the pharmaceutically acceptable hydrophilic polymers are selected from partially etherified cellulose derivatives, comprising carboxymethyl-, hydroxyethyl-, hydroxypropyl-, hydroxypropylmethyl-, or methyl-cellulose.

52. The formulation according to claim 5, wherein the completely synthetic hydrophilic polymers are selected from polyacrylates, polymethacrylates, poly(hydroxyethyl)-, poly(hydroxypropyl)-, poly(hydroxypropylmethyl)methacrylate, polyacrylonitrile, methallyl-sulphonate, polyethylenes, polyoxiethylenes, polyethylene glycols, polyethylene glycol-lactide, polyethylene glycol-diacrylate, polyvinylpyrrolidone, polyvinyl alcohols, poly(propylmethacrylamide), poly(propylene fumarate-co-ethylene glycol), poloxamers, polyaspartamide, hydrazine cross-linked hyaluronic acid and silicone.

53. The formulation according to claim 5, wherein the natural gums are selected from alginates, carrageenan, guar-gum, gelatine, tragacanth, amidated pectin, xanthan, chitosan collagen and agarose.

54. The formulation according to claim 7, wherein the synthetic phenolic antioxidants are selected from butylated hydroxyanisol (BHA), butylated hydroxytoluene (BHT) and di-tert-butylphenol (LY178002, LY256548, HWA-131, BF-389, CI-986, PD-127443, E-5119, BI-L-239XX), tertiary butylhydroquinone (TBHQ), propyl gallate (PG) and 1-O-hexyl-2,3,5-trimethylhydroquinone (HTHQ).

55. The formulation according to claim 7, wherein the aromatic amines are selected from diphenylamine, p-alkylthio-o-anisidine, ethylenediamine derivatives, carbazol and tetrahydroindenoindol.

56. The formulation according to claim 7, wherein the phenols and phenolic acids are selected from guaiacol, hydroquinone, vanillin, gallic acids and their esters, photocatechuic acid, quinic acid, syringic acid, ellagic acid, salicylic acid, nordihydroguaiaretic acid (NDGA) and eugenol.

57. The formulation according to claim 7, wherein the tocopherols and their derivatives are selected from tocopheryl-acrylate, -laurate, myristate, -palmitate, -oleate, -linoleate, or any other suitable tocopheryl-lipoate and tocopheryl-POE-succinate.

58. The formulation according to claim 7, wherein the ascorbic acids are selected from 6-o-lauroyl, myristoyl, palmitoyl-, oleoyl, or linoleoyl-L-ascorbic acid.

59. The formulation according to claim 7, wherein the non-steroidal anti-inflammatory agents (NSAIDs) are selected from indomethacine, diclofenac, mefenamic acid, flufenamic acid, phenylbutazone, oxyphenbutazone acetylsalicylic acid, naproxen, diflunisal, ibuprofene, ketoprofene, piroxicam, penicillamine, penicillamine disulphide, primaquine, quinacrine, chloroquine, hydroxychloroquine, azathioprine, phenobarbital and acetaminephen.

60. The formulation according to claim 7, wherein the antiarrhythmics are selected from amiodarone, aprindine and asocainol.

61. The formulation according to claim 7, wherein the calcium antagonists are selected from nifedipine, nisoldipine, nimodipine, nicardipine and nilvadipine.

62. The formulation according to claim 7, wherein the beta-receptor blockers are selected from atenolol, propranolol and nebivolol.

63. The formulation according to claim 7, wherein the chellating agents are selected from EDTA, GDTA and desferral.

64. The formulation according to claim 7, wherein the miscellaneous endogenous defense systems are selected from transferrin, lactoferrin, ferritin, cearuloplasmin, haptoglobion, haemopexin, albumin, glucose and ubiquinol-10.

65. The formulation according to claim 7, wherein the enzymatic antioxidants is superoxide dismutase.

66. The formulation according to claim 7, wherein the metal complexes are selected from catalase and glutathione peroxidase.

67. The formulation according to claim 7, wherein the less complex molecules are selected from beta-carotene, bilirubin and uric acid.

68. The formulation according to claim 7, wherein the flavonoids are selected from flavones, flavonols, flavonones, flavanonals, chalcones and anthocyanins.

69. The formulation according to claim 7, wherein the tannines, cinnamic acid, hydroxycinnamic acids and their esters are selected from coumaric acid and esters, caffeic acid and their esters, ferulic acid, (iso-)chlorogenic acid and sinapic acid.

70. The formulation according to claim 7, wherein the spice extracts are selected from spice extracts from clove, cinnamon, sage, rosemary, mace, oregano, allspice and nutmeg.

71. The formulation according to claim 7, wherein the oat flour extract is avenanthramide 1 or 2.

72. The formulation according to claim 7, wherein the steroid derivative is U74006F.

73. The formulation according to claim 7, wherein the tryptophan metabolites are selected from 3-hydroxykynurenine and 3-hydroxyanthranilic acid.

74. The formulation according to claim 9, wherein the short chain alcohols are selected from ethyl and isopropyl alcohol, chlorobutanol, benzyl alcohol, chlorobenzyl alcohol, dichlorobenzylalcohol and hexachlorophene.

75. The formulation according to claim 9, wherein the phenolic compounds are selected from cresol, 4-chloro-m-cresol, p-chloro-m-xlenol, dichlorophene, hexachlorophene and povidon-iodine.

76. The formulation according to claim 9, wherein the parabenes are selected from alkyl-parabenes, including methyl-, ethyl-, propyl-, or butyl- paraben and benzyl paraben.

77. The formulation according to claim 9, wherein the acids are selected from sorbic acid, benzoic acid and their salts.

78. The formulation according to claim 9, wherein the quaternary ammonium compounds are selected from alkonium salts, benzalkonium salts, cetrimonium salts, phenoalkecinium salts, phenododecinium bromide, cetylpyridinium chloride and other salts;

79. The formulation according to claim 9, wherein the benzalkonium salts are selected from benzalkonium chloride and benzalkonium bromide.

80. The formulation according to claim 9, wherein the mercurial compounds are selected from phenylmercuric acetate, borate, or nitrate, thiomersal, chlorhexidine or its gluconate, and mixtures thereof.

81. The formulation of claim 11, wherein the corticosteroids are selected from glucocorticoids or mineralocorticosteroids.

82. The formulation according to claim 39, wherein the corticosteroid is propionate.

VERSION WITH MARKINGS TO SHOW CHANGES MADE IN SPECIFICATION

Please note that additions to the specification are shown underlined and deletions are shown in brackets.

At page 1, lines 1-7:

Improved formulation for topical no-invasive application in vivo

This is a continuation of Application No. PCT/EP98/08421, filed December 23, 1998.

At page 6, beginning at line 5:

Convenient solutions with special properties are provided by the subject matters of the subclaims.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the results of biological experiments in which oedema-suppression activity of hydrocortisone in a commercial reference creme (open symbols) was tested against the same amount of identical drug in highly deformable lipid vesicles (Transfersomes) (closed symbols) in mice. The upper panel contains time-dependence ("pharmacodynamic") data, whereas the lower panel gives the dose dependency measured 16 h after the drug application. Data points give the mean values for 3-4 animals.

Figure 2 illustrates the suppression of the arachidonic acid-induced oedema by dexamethasone in a commercial creme (open symbols) or in Transfersomes (closed symbols) as a function of the time after drug administration (upper panel) or of the epicutaneously applied drug dose (lower panel).

Figure 3 provides information related to that given in figures 1 and 2, but pertaining to a different glucocorticosteroide, triamcinolone acetonide.

Figure 4 presents the results of dose and time dependence measurements for triamcinolone-acetonide applied in a commercial creme (open symbols) or in Transfersomes (closed symbols) on one forearm of a healthy human volunteer. The read-out was the extent of skin blanching caused by the drug, a the tested doses as given in insets.

Figure 5 shows dexamethasone penetration profile in murine skin in vivo (left panel) or in a pig skin ex vivo (right panel). Open symbols were measured with a commercial creme and closed symbols with the suspension of dexamethasone-loaded Transfersomes.

Figure 6 demonstrates the level of corticosteroid accumulation (retention) in the skin after different drugs' application on the organ surface by means of Transfersomes (closed down-arrow: the stratum corneum; closed up-arrow: the skin stripped free of the stratum corneum; open diamond: total drug amount in the entire skin (= the sum of the former two).

Figure 7 illustrates (pharmaco)kinetics of transcutaneous transport of various corticosteroids, as assessed by measuring the drug derived radioactivity in the serum, following the topical drug administration with ultradeformable vesicles on (closed symbols) or under (open symbols) intact murine skin. Data points give the mean values for 3-4 animals and vertical bars give standard error of the mean. The applied drug dose in relative units is given in insets.

Figure 8 provides some representative data on biological, anti-oedema activity of triamcinolone-acetonide applied on the skin in a commercial lotion or in conventional lipid vesicles, liposomes (lower panel) or else in highly deformable mixed lipid vesicles, Transfersomes (upper panel). All results were determined in the arachidonic acid induced murine ear oedema model. The topically applied doses are given in the panels. Formulation B was based on oleic acid rather than on phospholipids, as the main carrier ingredient.

Figure 9 shows the results of skin atrophy measurements in healthy human volunteers, treated for 6 weeks, twice daily, epicutaneously with two triamcinolone acetoneide formulations (TAC I and

TAC II), differing in antioxidant composition, as specified in Examples 53 - 56, "pre" relating to the pre-treatment phase, "rec" to the recovery phase, and "x" to the number of weeks of recovery.